Multiple functions of Cerberus cooperate to induce heart downstream of Nodal.

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Public Summary:

Scientific Abstract:
The TGFbeta family member Nodal has been implicated in heart induction through misexpression of a dominant negative version of the type I Nodal receptor (Alk4) and targeted deletion of the co-receptor Cripto in murine ESCs and mouse embryos; however, whether Nodal acts directly or indirectly to induce heart tissue or interacts with other signaling molecules or pathways remained unclear. Here we present Xenopus embryological studies demonstrating an unforeseen role for the DAN family protein Cerberus within presumptive foregut endoderm as essential for differentiation of cardiac mesoderm in response to Nodal. Ectopic activation of Nodal signaling in non-cardiogenic ventroposterior mesendoderm, either by misexpression of the Nodal homologue XNr1 together with Cripto or by a constitutively active Alk4 (caAlk4), induced both cardiac markers and Cerberus. Mosaic lineage tracing studies revealed that Nodal/Cripto and caAlk4 induced cardiac markers cell non-autonomously, thus supporting the idea that Cerberus or another diffusible factor is an essential mediator of Nodal-induced cardiogenesis. Cerberus alone was found sufficient to initiate cardiogenesis at a distance from its site of synthesis. Conversely, morpholino-mediated specific knockdown of Cerberus reduced both endogenous cardiomyogenesis and ectopic heart induction resulting from misactivation of Nodal/Cripto signaling. Since the specific knockdown of Cerberus did not abrogate heart induction by the Wnt antagonist Dkk1, Nodal/Cripto and Wnt antagonists appear to initiate cardiogenesis through distinct pathways. This idea was further supported by the combinatorial effect of morpholino-medicated knockdown of Cerberus and Hex, which is required for Dkk1-induced cardiogenesis, and the differential roles of essential downstream effectors: Nodal pathway activation did not induce the transcriptional repressor Hex while Dkk-1 did not induce Cerberus. These studies demonstrated that cardiogenesis in mesoderm depends on Nodal-mediated induction of Cerberus in underlying endoderm, and that this pathway functions in a pathway parallel to cardiogenesis initiated through the induction of Hex by Wnt antagonists. Both pathways operate in endoderm to initiate cardiogenesis in overlying mesoderm.